HEALTH EFFECTS OF

EXPOSURE TO

ENVIRONMENTAL TOBACCO SMOKE

FINAL DRAFT
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Preface

Environmental tobacco smoke (ETS), also called second hand tobacco smoke, can affect nonsmokers in proximity to people smoking tobacco. The scientific and medical literature contains numerous investigations of the association between ETS exposure and a variety of adverse health impacts, including carcinogenicity as well as cardiovascular, developmental, reproductive, and childhood respiratory effects. Although not all studies have shown an association, authoritative reviews over the past two decades have presented scientific evidence linking ETS exposures to a number of adverse health outcomes.

Interest in the health effects of second hand tobacco smoke on the part of members of the Scientific Review Panel (SRP) on Toxic Air Contaminants of the Air Resources Board (ARB) led to a request by the SRP for a health assessment of ETS, and a collaborative agreement between the Office of Environmental Health Hazard Assessment (OEHHA) and the ARB in February 1992 to initiate such an assessment. Although not formally entered into the State's Assembly Bill 1807 toxic air contaminant identification program, the ARB, SRP and OEHHA agreed that a thorough assessment of risk similar to that done under the AB 1807 process was warranted. This was done to ensure a thorough review of the scientific data, frequent public input through public comment periods and workshops, and an independent scientific review by the SRP.

Because the ARB has determined that this assessment is not part of the AB 1807 process and ETS is not being considered for formal identification as a toxic air contaminant by the ARB, this report will not be presented at a public hearing of the members of the Air Resources Board. Following both public review and comment, and peer review by the SRP, the final assessment along with all comments will be forwarded to the Department of Health Services (DHS) Tobacco Control Program for appropriate action under their mandate as the State's lead agency for addressing health effects related to tobacco use.

OEHHA, with the assistance of scientists from the DHS, had primary responsibility for the preparation of this assessment. ARB provided assistance with the ETS-related exposure data as well as with report reproduction, workshop organization, and mailouts.

OEHHA and ARB sponsored a workshop in October 1992 to obtain public input early in the evaluation of ETS health effects and exposure in California. At the workshop, preliminary thoughts on the direction of the ETS assessment were discussed with participants, which included individuals from local, state and federal government agencies, universities and other research organizations, representatives of the tobacco industry, and public interest groups.

The development of the assessment involved extensive literature review, document development, public workshops, public comment and scientific peer review followed by document revision. Public release of reviews on each major area of health effects

occurred as they were prepared. The first two documents (*Respiratory Health Effects of ETS* and *The Role of ETS in Cancers Other Than Lung Cancer*) were mailed in May 1994; subsequent documents were released in September 1994 (*Cardiovascular Health Effects of Exposure to ETS*), March 1995 (*Developmental and Reproductive Effects of Exposure to ETS*), September 1995 (*ETS: Exposure Measurements and Prevalence*), and January 1996 (*Carcinogenic Effects of Exposure to ETS, Excerpt: ETS and Lung Cancer*). Following a public comment period, each document was revised to respond to comments received and updated to include critical new studies; these revised documents have been compiled to form the current assessment. This most recent health assessment of ETS was extensively peer reviewed by Professor Stanton Glantz of the University of California at San Francisco and Professor Craig V. Byus of the University of California at Riverside, members of ARB's Scientific Review Panel, and Jennifer Jinot of U.S. EPA and co-author of U.S. EPA's 1992 report "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders". The chapter on carcinogenic effects of exposure to ETS was peer reviewed by Dr. Gary D. Friedman of the Permanente Medical Group and member of ARB's Scientific Review Panel and Dr. Kathryn E. Osann of the Department of Medicine, University of California at Irvine. The comments and suggestions from these reviewers have been addressed in this version of the health assessment of ETS.

The material comprising Chapters 2 to 8 has received internal and extensive external review through public workshops, meetings and written public comment, and reflects a number of changes made in response to comments received. To aid the reader of the current report, revisions to the chapters made after the external release are briefly outlined below. In addition, Appendix A summarizes written comments received from the public during the formal comment periods, as well as responses to those comments.

Chapter 2 on exposure measurement and prevalence was developed to provide background information on exposure measurement, emphasizing investigation and monitoring methods used in epidemiological evaluations of health effects. Information on prevalence of ETS exposure was also provided. In response to comments received suggesting that the document was being mistaken for a comprehensive exposure assessment, various wording changes were made to clarify the scope of the document. Regarding other specific changes, a study on DNA adducts of tobacco smoke constituents and the *p53* gene and recent studies on the prevalence of ETS exposure in California and the U.S. have been added. The current assessment takes the position that thiocyanate is not a very useful biomarker of ETS exposure. It also points out that while 3-ethenylpyridine, solanesol and ultraviolet particulate matter have been used by some researchers, they have not been widely adopted.

Chapters 3 to 5 were externally released as a single document, and many detailed changes were made to these three chapters in response to comments received. Several points of clarification were made to Chapter 3, on perinatal manifestations of developmental toxicity. Four additional published studies on fetal growth and home and work exposure to ETS, and two additional studies on fetal growth and biomarker measures were reviewed and described, and the discussion was expanded to reflect study findings.

Attributable risk calculations for ETS exposure and low birthweight were made. An additional study was included in the section on spontaneous abortion and perinatal mortality. In Chapter 4, on postnatal manifestations of developmental effects, a major change concerns the conclusion regarding the relationship between ETS exposure and sudden infant death syndrome (SIDS). Recently published studies on SIDS have been added, and the document now indicates that ETS exposure is causally associated with SIDS. Attributable risk calculations were provided for SIDS. In Chapter 5, on male and female reproductive effects, a definition of fecundability ratio is now given. A study on female fertility has been added.

Chapter 6, on respiratory effects, has been considerably enlarged, and several points of clarification added in response to comments. Additional recent studies have been reviewed. Major additions have been made to sections on asthma, lung function in children and cystic fibrosis. Medical terms are now defined as they are first used. The chapter now includes an explicit summary statement that published investigations on ETS exposure and atopy have produced mixed results.

Regarding revisions made to Chapter 7, on carcinogenic effects, the section on breast cancer has been expanded to describe recently published studies and discuss their implications. Clarifications regarding the U.S. EPA review of lung cancer and ETS have been made. The current chapter extends or modifies the discussion of issues related to ETS exposure and cervical cancer (*e.g.*, on confounders in epidemiological studies, active smoking, DNA adducts in cervical biopsies), nasal sinus cancer, and leukemia. Several studies on biomarkers of transplacental and early childhood exposure to ETS and two studies on brain cancer in children have been added.

A number of changes have been made to Chapter 8 on cardiovascular effects. Added material includes: a review of two recent analyses of the American Cancer Society CPS cohort, a discussion of a recent review and risk assessment on ETS exposure and cardiovascular effects, descriptions and a discussion of the implications of several additional case-control studies, sections on clinical observations regarding ETS exposure and internal and common carotid wall thickness and endothelial function, and description of findings from six additional laboratory studies on rodents and dogs.

Authors and Acknowledgements

This document was prepared by the Reproductive and Cancer Hazard Assessment Section (RCHAS) and the Air Toxicology and Epidemiology Section (ATES) within the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (Cal/EPA). Lauren Zeise was the project officer with overall responsibility for the contents of this report. Amy Dunn coordinated the development of the draft chapters and their revision, and the public workshops. James Donald played a key role in the planning and development of Chapters 3, 4 and 5. Amy Dunn and Lauren Zeise were the editors of this report.

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While OEHHA staff provided technical editing and incorporated reviewers' comments into each chapter to develop a comprehensive and consistent document, the following people were the primary authors:

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Contributors and Reviewers

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As described in the preface, this draft was preceded by External Review Drafts of each topic area which were released for public review and comment. The authors wish to thank those who sought to improve the quality of this report with their comments, and are particularly grateful to the members of the Scientific Review Panel, especially the leads on ETS, Stanton Glantz, Gary Friedman, Craig Byus, and Charles Becker (former panel member), who provided guidance and detailed suggestions. Special thanks to Jennifer Jinot and Steven Bayard of U.S. EPA, and Ira Tager, Kathy Hammond, Neil Benowitz, John Balmes and John Pierce. Thanks also go to James Collins, John Faust, Jeff Fowles, Martha Sandy and David Ting, for assistance with the response to public comments.

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Executive Summary

Exposure to environmental tobacco smoke (ETS) has been linked to a variety of adverse health outcomes. Many Californians are exposed at home, at work and in public places. In the comprehensive reviews published as *Reports of the Surgeon General* and by the U.S. Environmental Protection Agency (U.S. EPA) and the National Research Council (NRC), ETS exposure has been found to be causally associated with respiratory illnesses, including lung cancer, childhood asthma and lower respiratory tract infections. Scientific knowledge about ETS-related effects has expanded considerably since the release of these reviews. The State of California has therefore undertaken a broad review of ETS, covering the major health endpoints potentially associated with ETS exposure: perinatal and postnatal manifestations of developmental toxicity, adverse impacts on male and female reproduction, respiratory disease, cancer, and cardiovascular disease. A "weight of evidence" approach has been used to describe the body of evidence for an effect and to support a conclusion as to whether ETS exposure is causally associated with a particular effect. Because the epidemiological data are extensive, they serve as the primary basis for assessment of ETS-related effects in humans. The report also presents an overview on measurements of ETS exposure, particularly as they relate to characterizations of exposure in epidemiological investigations, and on the prevalence of ETS exposure in California and nationally.

ETS, or "secondhand smoke", is the complex mixture formed from the escaping smoke of a tobacco product, and smoke exhaled by the smoker. The characteristics of ETS change as it ages and combines with other constituents in the ambient air. Exposure to ETS is also frequently referred to as "passive smoking", or "involuntary tobacco smoke" exposure. Although all exposures of the fetus are "passive" and "involuntary", for the purposes of this review *in utero* exposure resulting from maternal smoking during pregnancy is not considered to be ETS exposure.

General Findings

ETS is an important source of exposure to toxic air contaminants indoors. Despite an increasing number of restrictions on smoking and increased awareness of health impacts, exposures in the home, especially of infants and children, continue to be a public health concern. ETS exposure is causally associated with a number of health effects. Listed in Table ES.1 are the developmental, respiratory, carcinogenic and cardiovascular effects for which there is sufficient evidence of a causal relationship, including fatal outcomes such as sudden infant death syndrome and heart disease mortality, as well as serious chronic diseases such as childhood asthma. There are in addition effects for which evidence is suggestive of an association but further research is needed for confirmation. These include spontaneous abortion, cervical cancer, and exacerbation of asthma in adults (Table ES.1). Finally, it is not possible to judge on the basis of the current evidence the impact of ETS on a number of endpoints, including congenital malformations, changes in female

fertility and fecundability, male reproductive effects, rare childhood cancers and cancers of the bladder, breast, stomach, brain, hematopoietic system, and lymphatic system.

TABLE ES.1
HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

Effects Causally Associated with ETS Exposure

Developmental Effects
Fetal Growth: Low birthweight or small for gestational age
Sudden Infant Death Syndrome (SIDS)

Respiratory Effects
Acute lower respiratory tract infections in children (*e.g.*, bronchitis and pneumonia)
Asthma induction and exacerbation in children
Chronic respiratory symptoms in children
Eye and nasal irritation in adults
Middle ear infections in children

Carcinogenic Effects
Lung Cancer
Nasal Sinus Cancer

Cardiovascular Effects
Heart disease mortality
Acute and chronic coronary heart disease morbidity

Effects with Suggestive Evidence of a Causal Association with ETS Exposure

Developmental Effects
Spontaneous abortion
Adverse impact on cognition and behavior

Respiratory Effects
Asthma exacerbation in adults
Exacerbation of cystic fibrosis
Decreased pulmonary function

Carcinogenic Effects
Cervical cancer

Many Californians are exposed to ETS, and the number of people adversely affected may be correspondingly large. Table ES.2 presents morbidity and mortality estimates for health effects causally associated with ETS exposure. For cancer, cardiovascular and some respiratory endpoints, estimates are derived from figures published for the U.S. population, assuming that the number affected in California would be 12% of the total. The estimates for middle ear infection, sudden infant death syndrome and low birthweight were derived using information on prevalence of ETS exposure in California and the U.S.

TABLE ES.2

ESTIMATED ANNUAL MORBIDITY AND MORTALITY IN NONSMOKERS ASSOCIATED WITH ETS EXPOSURE

Condition	Number of People or Cases	
	in the U.S.	in California[a]
Developmental Effects		
Low birthweight	≈ 9,700 - 18,600 cases	≈ 1,200 - 2,200 cases
Sudden Infant Death Syndrome (SIDS)	≈ 1,900 - 2,700 deaths	≈ 120 deaths
Respiratory Effects in Children		
Middle ear infection	0.7 to 1.6 million physician office visits	78,600 to 188,700 physician office visits
Asthma induction	8,000 to 26,000 new cases	960 to 3120 new cases
Asthma exacerbation	400,000 to 1,000,000 children	48,000 to 120,000 children
Bronchitis or pneumonia in infants and toddlers (18 months and under)	150,000 to 300,000 cases 7,500 to 15,000 hospitalizations 136 - 212 deaths	18,000 to 36,000 cases 900 to 1800 hospitalizations 16 - 25 deaths
Cancer		
Lung	3000 deaths	360 deaths
Nasal sinus	N/A[b]	N/A[b]
Cardiovascular Effects		
Ischemic heart disease	35,000 - 62,000 deaths	4,200 - 7,440 deaths

[a] California predictions are made by multiplying the U.S. estimate by 12%, the fraction of the U.S. population residing in the State. The exceptions are California estimates for low birthweight, SIDS, and otitis media which are provided in Chapters 3, 4, and 6 respectively. For these cases the sources cited provided the odds or risk ratios serving as the basis for the analyses.
[b] Estimates of the impact of ETS exposure on the occurrence of nasal sinus cancers are not available at this time.

Relative risk estimates associated with some of these endpoints are small, but because the diseases are common the overall impact can be quite large. A relative risk estimate of 1.3 for heart disease mortality in nonsmokers is supported by the collective evidence; this corresponds to a lifetime risk of death of roughly 1 to 3% for exposed nonsmokers and perhaps 4,000 deaths annually in California. The relative risk estimate of 1.2 to 1.4 associated with low birthweight implies that ETS may impact fetal growth of 1,200 to 2,200 newborns in California, roughly 1 to 2% of newborns of nonsmokers exposed at home or work. ETS may exacerbate asthma (RR ≈ 1.6 to 2) in 48,000 to 120,000 children in California. Large impacts are associated with relative risks for respiratory effects in children such as middle ear infection (RR ≈ 1.62), and lower respiratory disease in young children (RR ≈ 1.5 to 2). Asthma induction (RR ≈ 1.75 to 2.25) may occur in as many as 0.5 to 2% of ETS-exposed children. ETS exposure may be implicated in 120 SIDS deaths per year in California (RR ≈ 3.5), with a risk of death to 0.1% of infants exposed to ETS in their homes. Lifetime risk of lung cancer death related to ETS-exposed nonsmokers may be about 0.7% (RR ≈ 1.2). For nasal sinus cancers, observed relative risks have ranged from 1.7 to 3.0, but future studies are needed to confirm the magnitude of ETS-related risks.

Specific Findings and Conclusions

Exposure Measurement and Prevalence

ETS is a complex mixture of chemicals generated during the burning and smoking of tobacco products. Chemicals present in ETS include irritants and systemic toxicants such as hydrogen cyanide and sulfur dioxide, mutagens and carcinogens such as benzo(a)pyrene, formaldehyde and 4-aminobiphenyl, and the reproductive toxicants nicotine, cadmium and carbon monoxide. Many ETS constituents have been identified as hazardous by state, federal and international agencies. To date, over 50 compounds in tobacco smoke have been identified as carcinogens and six as developmental or reproductive toxicants under California's Proposition 65 (California Health and Safety Code 25249.5 *et seq*.).

Exposure assessment is critical in epidemiological investigations of the health impacts of ETS, and in evaluating the effectiveness of strategies to reduce exposure. Exposure can be assessed through the measurement of indoor air concentrations of ETS constituents, through surveys and questionnaires, or more directly through the use of personal monitors and the measurement of biomarkers in saliva, urine and blood. There are advantages and disadvantages associated with the various techniques, which must be weighed in interpreting study results. One important consideration in epidemiologic studies is misclassification of exposure. Studies on the reliability of questionnaire responses indicate qualitative information obtained is generally reliable, but that quantitative information may not be. Also, individuals are often unaware of their ETS exposure, particularly outside the home. In studies using both self-reporting and biological markers, the exposure prevalence was higher when determined using biological markers.

Available data suggest that the prevalence of ETS exposure in California is lower than elsewhere in the U.S. Among adults in California, the workplace, home and other indoor locations all contribute significantly to ETS exposure. For children the most important single location is the home. Over the past decade ETS exposures in California have decreased significantly in the home, workplace and in public places. Over the same period, restrictions on smoking in enclosed worksites and public places have increased (*e.g.*, Gov. Code, Section 19994.30 and California Labor Code, Section 6404.5) and the percentage of the adults who smoke has declined. Decreases in tobacco smoke exposure may not be experienced for some population subgroups, as patterns of smoking shift with age, race, sex and socioeconomic status. For example, from 1975 to 1988, the overall smoking prevalence among 16 to 18 year olds declined, but after 1988 the trend reversed.

Perinatal Manifestations of Developmental Toxicity

ETS exposure adversely affects fetal growth, with elevated risks of low birth weight or "small for gestational age" observed in numerous epidemiological studies. The primary effect observed, reduction in mean birthweight, is small in magnitude. But if the distribution of birthweight is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birthweight is associated with many well-recognized problems for infants, and is strongly associated with perinatal mortality.

The impact of ETS on perinatal manifestations of development other than fetal growth is less clear. The few studies examining the association between ETS and perinatal death are relatively non-informative, with only two early studies showing increased risk associated with parental smoking, and with the sparse data on stillbirth not indicative of an effect. Studies on spontaneous abortion are suggestive of a role for ETS, but further work is needed, particularly as a recent report did not confirm the findings of four earlier studies. Although epidemiological studies suggest a moderate association of severe congenital malformations with paternal smoking, the findings are complicated by the use of paternal smoking status as a surrogate for ETS exposure, since a direct effect of active smoking on sperm cannot be ruled out. In general, the defects implicated differed across the studies, with the most consistent association seen for neural tube defects. At this time, it is not possible to determine whether there is a causal association between ETS exposure and this or other birth defects.

Postnatal Manifestations of Developmental Toxicity

Numerous studies have demonstrated an increased risk of sudden infant death syndrome, or "SIDS," in infants of mothers who smoke. Until recently it has not been possible to separate the effects of postnatal ETS exposure from those of prenatal exposure to maternal active smoking. Recent epidemiological studies now have demonstrated that postnatal ETS exposure is an independent risk factor for SIDS.

Although definitive conclusions regarding causality cannot yet be made on the basis of available epidemiological studies of cognition and behavior, there is suggestive evidence that ETS exposure may pose a hazard for neuropsychological development. With respect to physical development, while small but consistent effects of active maternal smoking during pregnancy have been observed on height growth, there is no evidence that postnatal ETS exposure has a significant impact in otherwise healthy children. As discussed in greater detail below, developmental effects of ETS exposure on the respiratory system include lung growth and development, childhood asthma exacerbation, and, in children, acute low respiratory tract illness, middle ear infection and chronic respiratory symptoms.

Female and Male Reproductive Toxicity

Though active smoking by women has been found to be associated with decreased fertility in a number of studies, and tobacco smoke appears to be anti-estrogenic, the epidemiological data on ETS exposure and fertility are not extensive and show mixed results, and it is not possible to determine whether ETS affects fecundability or fertility. Regarding other female reproductive effects, while studies indicate a possible association of ETS exposure with early menopause, the analytic methods of these studies could not be thoroughly evaluated, and therefore at present, there is not firm evidence that ETS exposure affects age at menopause. Although associations have been seen epidemiologically between active smoking and sperm parameters, conclusions can not be made regarding ETS exposure and male reproduction, as there is very limited information available on this topic.

Respiratory Effects

ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract. In children, ETS exposure can exacerbate asthma, and increases the risk of lower respiratory tract illness, and acute and chronic middle ear infection. ETS may also exacerbate asthma in adults. Eye and nasal irritation are the most commonly reported symptoms among adult nonsmokers exposed to ETS. Odor annoyance has been demonstrated in several studies.

Regarding chronic health effects, there is compelling evidence that ETS is a risk factor for induction of new cases of asthma as well as for increasing the severity of disease among children with established asthma. In addition, chronic respiratory symptoms in children, such as cough, phlegm, and wheezing, are associated with parental smoking. While the results from all studies are not wholly consistent, there is evidence that childhood exposure to ETS affects lung growth and development, as measured by small, but statistically significant decrements in pulmonary function tests; associated reductions may persist into adulthood. The effect of chronic ETS exposure on pulmonary function in otherwise healthy adults is likely to be small, and unlikely by itself to result in clinically significant chronic disease. However, in combination with other insults (*e.g.*, prior smoking history, exposure to occupational irritants or ambient air pollutants), ETS

exposure could contribute to chronic respiratory impairment in adults. In addition, regular ETS exposure in adults has been reported to increase the risk of occurrence of a variety of lower respiratory symptoms.

Children are especially sensitive to the respiratory effects of ETS exposure. Children with cystic fibrosis are likely to be more sensitive than healthy individuals. Several studies of patients with cystic fibrosis, a disease characterized by recurrent and chronic pulmonary infections, suggest that ETS can exacerbate the condition. Several studies have shown an increased risk of atopy (a predisposition to develop IgE antibodies against common allergens, which can then be manifested as a variety of allergic conditions) in children of smoking mothers, though the evidence regarding this issue is mixed.

Carcinogenic Effects

The role of ETS in the etiology of cancers in nonsmokers was explored, as smoking is an established cause of a number of cancers (lung, larnyx, oral cavity, esophagus and bladder), and a probable cause of several others (cervical, kidney, pancreas, and stomach). Also, ETS contains a number of constituents which have been identified as carcinogens.

Reviews published in the 1986 *Report of the Surgeon General*, by the National Research Council in 1986, and by the U.S. EPA in 1992 concluded that ETS exposure causes lung cancer. Three large U.S. population-based studies and a smaller hospital-based case control study have been published since the completion of the U.S. EPA review. The population-based studies were designed to and have successfully addressed many of the weaknesses for which the previous studies on ETS and lung cancer have been criticized. Results from these studies are compatible with the causal association between ETS exposure and lung cancer already reported by the U.S. EPA, Surgeon General, and National Research Council. Of the studies examining the effect of ETS exposure on nasal sinus cancers, all three show consistent associations, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults. Further study is needed to characterize the magnitude of the risk of nasal sinus cancer from ETS exposure.

The epidemiological and biochemical evidence suggest that exposure to ETS may increase the risk of cervical cancer. Positive associations were observed in two of three case-control studies and a statistically nonsignificant positive association was observed in the only cohort study conducted. Findings of DNA adducts in the cervical epithelium as well as nicotine and cotinine in the cervical mucus of ETS-exposed nonsmokers provides biological plausibility.

For other cancer sites in adults, there has been limited ETS-related epidemiological research in general: there is currently insufficient evidence to draw any conclusion regarding the relationship between ETS exposure and the risk of occurrence. A review of the available literature clearly indicates the need for more research. For example, although compounds established as important in the etiology of stomach cancer are present in tobacco smoke, only a single cohort study has been performed for this site. Precursors of

endogenously formed N-nitroso compounds suspected of causing brain tumors are present in high concentrations in ETS, and the one cohort and two case-control studies available suggest a positive association, but the results are based on small numbers and may be confounded by active smoking. In biochemical studies of nonsmokers, higher levels of hemoglobin adducts of the established bladder carcinogen, 4-aminobiphenyl, have been found in those exposed to ETS. However, no significant increases in bladder cancer were seen in the two epidemiological studies (case-control) conducted to date, although both studies were limited in their ability to detect an effect. Several compounds in tobacco smoke are associated with increased risk of leukemia, but only one small case-control study in adults, reporting an increased risk with ETS exposure during childhood, has been performed. Finally, all four studies on ETS exposure and breast cancer suggest an association, but in two of the studies the associations were present only in select groups, and in three studies there is either no association between active smoking and the risk of breast cancer or the association for active smoking is weaker than for passive smoking. Moreover, there is no indication of increasing risk with increasing intensity of ETS exposure. Still, results from a recent study suggest that tobacco smoke may influence the risk of breast cancer in certain susceptible groups of women, and this requires further investigation.

Regarding childhood cancers, it is unclear whether parental smoking increases risk overall, or for specific cancers such as acute lymphoblastic leukemia and brain tumors, the two most common cancers in children. The lack of clarity is due to the conflicting results reported and the limitations of studies finding no association. The epidemiological data on ETS exposure and rare childhood cancers also provide an inadequate foundation for making conclusions regarding causality. Some studies found small increased risks in children in relation to parental smoking for neuroblastoma, Wilm's tumor, bone and soft-tissue sarcomas, but not for germ cell tumors. Studies to date on these rare cancers have been limited in their power to detect effects. The impact of ETS exposure on childhood cancer would benefit from far greater attention than it has received to date.

Cardiovascular Effects

The epidemiological data, from prospective and case-control studies conducted in diverse populations, in males and females and in western and eastern countries, are supportive of a causal association between ETS exposure from spousal smoking and coronary heart disease (CHD) mortality in nonsmokers. To the extent possible, estimates of risk were determined with adjustment for demographic factors, and often for other factors related to heart disease, such as blood pressure, serum cholesterol level and obesity index. Risks associated with ETS exposure were almost always strengthened by adjustment for other cofactors. For nonsmokers exposed to spousal ETS compared to nonsmokers not exposed, the risk of CHD mortality is increased by a factor of 1.3. The association between CHD and risk is stronger for mortality than for non-fatal outcomes, including angina.

Data from clinical studies suggest various mechanisms by which ETS causes heart disease. In a number of studies in which nonsmokers were exposed to ETS, carotid wall thickening and compromise of endothelial function were similar to, but less extensive than those experienced by active smokers. Other effects observed include impaired exercise performance, altered lipoprotein profiles, enhanced platelet aggregation, and increased endothelial cell counts. These findings may account for both the short- and long-term effects of ETS exposure on the heart.